

4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention

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The first IAS conference to highlight biomedical prevention was held in Sydney in July 2007

Over 5000 delegates from 133 countries met in Sydney in July for the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, the first major international conference on the biomedical aspects of AIDS to be held in Australia. It was also the first conference in this series to include prevention in its title and to assign a central role to prevention research in the scientific program, alongside basic science and clinical research. Coinciding with the conference was the release of the Sydney Declaration, which calls for 10% of all resources devoted to HIV programming to be dedicated to research¹ (Box). The conference provided Australia with an opportunity to benefit from the presence of world-leading scientists from a number of disciplines, as well as to showcase outstanding Australian achievements in HIV research.

Clinical research, treatment and care

According to the World Health Organization, the number of people receiving antiretroviral therapy (ART) worldwide now exceeds two million, which represents 28% of the adults, but only 15% of the children, who urgently need treatment in low- and middle-income countries. Debrework Zewdie (Director, Global HIV/AIDS Program, World Bank, Washington, DC, USA) reported that, as ART rollout continues at a fast pace in developing countries, new challenges are being recognised, including the “brain drain” of health professionals, limited laboratory facilities to monitor treatment, lack of access to the more costly regimens that limit toxicity or act as second-line treatment regimens, the coincident epidemic of tuberculosis fuelled by both the HIV epidemic and increasing resistance to standard antituberculosis drugs, and the need to increase coverage to include the most vulnerable, including injecting drug users (conference abstract MOPL1, available online at the conference website²).

The conference highlighted research on new agents and new ways of using existing drugs to improve clinical outcomes. New drugs included etravirine (active against HIV resistant to first-line non-nucleoside reverse transcriptase inhibitors) (abstracts WESS204-1 and WESS204-2), raltegravir (the first integrase inhibitor) (abstract TUAB104), and maraviroc (the first chemokine inhibitor) (abstract WESS104), all of which showed efficacy in Phase III clinical trials. Patients with multidrug-resistant HIV following treatment with existing drug classes can now expect, in well resourced countries, to achieve full viral suppression with the newer agents. Other ART agents in earlier phases of development include apricitabine (abstract WESS203), active against lamivudine-resistant HIV, and being developed by an Australian pharmaceutical company, and PRO 140, a CCR5 monoclonal antibody, which could potentially be administered subcutaneously once weekly (abstract WESS201).

The long-standing debate about when to start ART was reignited during the conference. The Children with HIV Early Antiretroviral Therapy (CHER) study in South Africa enrolled 252 infants less than 12 weeks of age and randomly assigned them to start ART immediately or defer therapy for 1–2 years. It was halted after an interim analysis

revealed a 75% reduction in mortality in the immediate therapy arm (abstract WESS103). In adults, there is mounting evidence that ART should be initiated earlier than is recommended by the current guidelines (at CD4 T cell counts of 200–350 cells/ μ L),³ and new analyses of the landmark SMART (Strategies for Management of Antiretroviral Therapy) study⁴ found that patients who interrupted ART, even with a relatively intact immune system, were at increased excess risk of serious illness such as AIDS-defining conditions, malignancy and death from a number of causes including liver and cardiovascular disease, malignancy and AIDS.

After several years in which a cautious approach held sway, the pendulum now seems to be swinging back to earlier initiation of treatment. The immunological rationale for this has become clearer: the newer treatments are less toxic so can be taken for longer without the severe side effects of the older agents, and there is an increasing recognition of the public health benefit of early treatment in reducing infectiousness through viral suppression.

Biomedical prevention

There was much to discuss in the field of biomedical prevention, as the past year has witnessed some outstanding successes as well as some major setbacks.

In a compelling plenary address, Robert Bailey (Professor of Epidemiology, School of Public Health, University of Illinois, Chicago, USA) reviewed evidence from recent randomised trials of the strong protective effects of male circumcision against HIV acquisition (abstract TUPL101). While urging rapid scale-up in high prevalence settings, Bailey cautioned that circumcision needs to be integrated with broader HIV prevention strategies. Observational studies in Sydney (abstract WEAC103) and Peru (abstract WEAC102) showed no significant protective effect of circumcision in gay men.

The MIRA (Methods for Improving Reproductive Health in Africa) trial of female diaphragms in African women was concluded with a finding of no benefit (abstract WESS304). Retention rates were high in this long-term study (abstract TUAC104), but low adherence and reduced condom use in the diaphragm arm may have limited the study's ability to detect an effect. Similarly, no impact on HIV incidence was seen in a trial of daily acyclovir to suppress herpes simplex virus type 2 conducted among women in northern Tanzania (abstract MOAC104), although adherence may have also played a role in compromising the results of this study.

The conference heard new details about the two Phase III trials of cellulose sulfate gel as a vaginal microbicide which were suspended early this year. One trial, conducted in Africa and India, was halted after interim analyses revealed a more than twofold increased risk of HIV seroconversion among women using the gel, for reasons which remain unclear (abstract WESS301). The second trial was stopped, even though no differences in risk had been observed (abstract WESS302). At the other end of the development pathway, a Melbourne-based biotechnology company found that its candidate micro-

The Sydney Declaration: good research drives good policy and programming — a call to scale up research^{1*}

Ten per cent of all resources dedicated to HIV programming should be used for research towards optimizing interventions utilized and health outcomes achieved.

The evolution of HIV prevention, treatment, and care over the past quarter century is one of the great successes of medical science. Committed and sustained research efforts have provided the evidence on which approaches to programming are based. These same scientific efforts are now resulting in new prevention technologies and drugs, and new strategies to manage and deliver both. Good research drives good policy.

In recent years, resources have dramatically increased for delivery of existing interventions in resource-limited settings. Although funding remains insufficient to meet the increasing need for services, it is imperative that the global community does not lose sight of the future while responding to the immediate crisis. An effective response to HIV/AIDS requires a sustained commitment to ensure that interventions and approaches to service delivery are continuously improved over time. For example, as current first-line antiretroviral regimens become increasingly available in resource-limited settings, there is an urgent need to identify optimum, durable, and well-tolerated standardised first-line and second-line regimens, and to monitor and respond to resistance patterns as they emerge. Outcomes will not necessarily be the same in diverse settings across the globe.

Operations research is critical, in addition to basic, clinical, prevention, social, and policy research. We must identify which approaches are effective in the field, which are not, and why. We must also learn how to integrate HIV-specific services with primary, tuberculosis, malaria, prenatal and postnatal, and sexual and reproductive health services. None of these services have been as effectively linked to scale-up of HIV programming as is possible or necessary. Furthermore, greater understanding of the social, political, and cultural barriers that perpetuate stigma and discrimination can contribute to ensuring that governments act in the interests of public health.

Operations research will enable rapid implementation of new technologies to prevent, diagnose, and treat HIV infection, and can help to ensure that health systems are strengthened as a result of scaling-up HIV prevention, treatment, and care. Unfortunately, few granting agencies or national health budgets commit designated funds to operations research, and where such funding is available, it is often underused. The Global Fund to Fight AIDS, Tuberculosis and Malaria, for example, allows up to 10% of each grant to be allocated for operations research, but this provision is rarely used by countries and the research community is rarely represented on Country Coordinating Mechanisms (CCMs). The lack of participation on CCMs further reduces the likelihood that operations research will be a priority in funding applications.

An ancillary benefit of integrating research into the overall approach to scale-up in the developing world will be an expanding cadre of health-care workers trained in research methodologies and practice. Such research should not be seen as an additional burden on the various funding bodies or ministries of health but, on the contrary, as the only means by which we can refine our understanding of what is and is not effective.

Last but not least, all areas of research can further strengthen the efforts of the global AIDS community to confront the absurd theories of AIDS denialists as well as the “magic” cures that continue to confuse policymakers, health-care professionals, and communities of people at risk of and living with HIV/AIDS throughout the world. HIV professionals must continuously build on the evidence base to ensure sound and effective policies and practices in HIV/AIDS prevention, treatment, and care.

The undersigned individuals and organisations call on national governments and bilateral, multilateral, and private donors to allocate 10% of all resources for HIV programming to research. We believe that without such funding we will fail to maintain a sustained and effective response to the AIDS pandemic.

* As of 15 August 2007, there were 1854 signatories to the Sydney Declaration.



bicide, SPL7013 gel, was well tolerated in a penile application safety study, paving the way for trials in sexually active women (abstract TUAC11B).

Preventing maternal HIV transmission continued to advance with the finding from Tanzania (abstract TUAX101) and Rwanda (abstract TUAX102) that fewer than 1% of infants whose mothers received postpartum ART were infected with HIV during the breastfeeding period.

Supported by recently issued guidelines from the WHO and the United States Centers for Disease Control and Prevention, provider-initiated testing programs have increased the numbers of people tested in the US (abstract TUSY203) and Botswana (abstract TUSY205), and rapid testing has facilitated the return of results (abstract TUSY203). There is nevertheless ongoing controversy about this approach because of its “opt out” nature, particularly in settings where HIV-related stigma, discrimination and limited access to treatment remain realities.

Despite the undeniable importance of sexual transmission of HIV globally, intravenous drug use accounts for 10% of the global burden of HIV infection and is the leading mode of exposure in parts of Asia and eastern Europe. Data from Australia showed low and declining HIV prevalence among intravenous drug users, confirming our success in averting an epidemic in this population (abstract MOAC202) through harm-reduction strategies, particularly needle and syringe distribution. Thomas Kerr (Assistant Professor, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada) also reported a strong relation-

ship between efforts to decentralise the distribution of clean needles and syringes and reduced HIV injection risk behaviour in Canada (abstract MOAC205). However, a powerful presentation by Mauro Guarinieri (Chair of the Global Board of the Global Network of People Living with HIV/AIDS) reminded us that such strategies remain largely unavailable in many regions, and that the emphasis on drug prohibition has led to human rights violations and continues to impede efforts to prevent HIV among people who inject drugs (abstract TUSY303).

A safe and effective prophylactic vaccine remains the best hope for HIV prevention in the long term but seems as elusive as ever. Ongoing Phase IIb vaccine studies (abstract MOBS301-4) are investigating candidates that boost cellular immune responses and are expected to work by controlling HIV disease progression in those who become infected. The public health benefits of such vaccines could nevertheless include lower rates of illness, reduced potential for HIV transmission, and prolongation of the time to ART initiation.

“Lessons learned” from HIV prevention trials were also shared at the conference, with presentations reporting that willingness to participate in trials does not necessarily translate into participation (abstract TUPDC01), and that providing information to trial participants in a focused, locally appropriate manner and within a continuous informed consent framework improves comprehension and message retention (abstract MOAC303). Susan Kippax (Director, National Centre in HIV Social Research, University of New South Wales, Sydney, Australia) reminded us that there are many areas in which further research is

needed, including the meanings attributed to prevention technologies, expectations in relation to their effectiveness, and the impact of new and generally experimental prevention technologies on older, proven ones, such as condoms (abstract TUSY302).

Basic science

HIV immunopathogenesis represents a complex interplay between the virus and the host's immune response, and presentations from Michael Lederman (Director, Center for AIDS Research, Case Western Reserve University, Cleveland, USA; abstract MOPL102) and Jason Brechley (Research Fellow, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA; abstract TUSY402) crystallised current knowledge in this area. The pivotal event early in HIV infection is the massive depletion of mucosal CD4+ T cells that results in immunological and physical damage to the gastrointestinal tract, leading in turn to leakage of components from normal gut microorganisms into the blood. These microbial products stimulate the production of inflammatory cytokines from cells of the innate immune system, triggering T cell activation and expansion, and creating a greater pool of target cells to support HIV replication, ultimately resulting in the depletion of CD4+ T cells and lymph node fibrosis. Strategies to prevent immune activation are now being pursued in order to limit this HIV-mediated damage.

An area of intense investigation, critical for developing successful microbicides, is mucosal immunity. A study presented by Dr Maddy Hayes (St George's University of London, UK) demonstrated using human cervicovaginal tissue that a protein with anti-HIV properties could be elicited from these tissues by a mechanism that is independent of triggering known Toll-like receptors in cells of the innate immune system (abstract MOPDA02). This study raises the possibility of inducing endogenous antiviral factors as mucosal stimulants of the innate immune response. In a macaque study, Eric Arts (Assistant Professor, Division of Infectious Diseases, Case Western Reserve University, Cleveland, USA) demonstrated for the first time that a vaginally applied candidate microbicide (abstract PSC-RANTES) could select for a drug-resistant virus (abstract WESS303). Major implications of this study include the possibility that agents with different drug-resistance profiles should be considered for therapy versus prevention, and the importance of using a combination of drugs in topical microbicides to limit the emergence of HIV drug resistance.

The session on new drug targets and compounds highlighted novel approaches for inhibiting HIV replication. Orally bioavailable fusion inhibitors have been identified that have mechanisms of action unlike that of enfuvirtide, the first and currently only available drug in this class (abstract MOPDX01). A novel inhibitor, BIT225, developed by an Australian company, specifically inhibits HIV replication in macrophages, which represent a reservoir for HIV (abstract MOPDX06). An exciting HIV gene therapy approach using a "triple-R" vector was also presented by John Rossi (Professor and Chair of the Division of Molecular Biology, Beckman Research Institute, California, USA). This vector expresses a combination of three types of RNA to target essential viral genes and inhibit expression of the CCR5 host cell receptor, which is critical for viral entry (abstract TUPL102).

Conclusions

The Sydney conference provided an important opportunity for delegates from Australia and the region to participate in an international forum. Treatment access is expanding steadily but encountering practical barriers, and prevention science is entering a new era, with results

from recent trials raising complex implementation issues. In the absence of substantial increases in investment in both research and community building, the efficacy-effectiveness gap is likely to remain very wide. As we look forward to the 5th International AIDS Society Conference in South Africa, we would do well both to put the Sydney Declaration into practice and to heed the words of Maura Elaripe, of Igat Hope, the national network of HIV-positive people in Papua New Guinea, at the conference opening ceremony: "Talk with us, not about us".

Competing interests

Lisa Maher and John Kaldor are principal investigators on the male tolerance study of Vivagel (a candidate vaginal microbicide) mentioned in the article (abstract TUAC1LB); this was funded by a National Institutes of Health contract awarded to Starpharma. Iona Millwood is a researcher employed by the University of New South Wales, Sydney, on this study.

Gilda Tachedjian owns AVEXA shares, is currently a consultant for Starpharma and was a consultant for Biotron in 2006.

Jennifer Hoy is responsible for the clinical trial activities performed in the HIV service of the Alfred Hospital, Melbourne, and was reimbursed for the conduct of clinical trials involving etravirine, raltegravir, maraviroc and apricitabine. She received travel assistance from Pfizer (manufacturer of maraviroc) to attend the 2007 Conference on Retroviruses and Opportunistic Infections in Los Angeles, USA.

As rapporteur for the International AIDS Society meeting, which is the subject of this article, Anthony Jaworowski received accommodation and air fares from the conference organisers but not from any company or persons mentioned in this report.

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